Vascular complications of bee and wasp stings are rare. Cerebral infarction has only been reported in three other people.[2 3] In one three wasp stings were followed by collapse and a tonic-clonic seizure. Hypotension was not recorded. He was treated with adrenaline, barbiturates, and steroids. It is unclear whether the development of a hemiparesis preceded or followed this treatment. Brain CT confirmed cerebral infarction. Both other patients died after bee or wasp stings. At postmortem cerebral infarction was found in both.[3] The mechanism of cerebral infarction was not alluded to.

Acute myocardial infarction has been reported four times.[4] It has been suggested that this may be due to a combination of coronary vasoconstriction secondary to mediators released after wasp sting, aggravated by exogenous adrenaline given as part of the treatment and by platelet aggregation.[4 5] It is likely that the mechanism of cerebral infarction in this patient was similar. Wasp venom contains vasoactive, inflammatory, and thrombogenic peptides and amines, including histamine, leucotrienes, and thromboxane. The venom also contains allergenic proteins such as phospholipases which elicit an IgE response, resulting in mast cell activation.[6] Mast cell activation results in release of preformed substances such as histamine as well as de novo synthesis of other mediators. Constriction of coronary arteries has been shown to occur in response to histamine.[7] Both thromboxane and leucotrienes have been shown to be vasoconstrictors.[8] The adrenaline that the patient was given may also have been implicated in vasoconstriction, resulting in her cerebral infarct. Many of the factors released, including thromboxane and leucotrienes, cause platelet aggregation resulting in a prothrombotic state.

The other neurological complications of stings which have been reported are individual cases of ocular myasthenia gravis,[9] optic neuritis, limb numbness, and trigeminal neuralgia[10] and three cases of encephalopathy, one of which was fatal.[11] Postulated mechanisms include both a toxic effect of venom[9] and hypersensitivity to venom.[10 11]

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Cerebrospinal fluid manganese concentrations in patients with symmetric pallidal hyperintensities on T1 weighted MRI

Recently, there have been some reports that MRI shows characteristic brain lesions in patients with parenteral nutrition containing manganese (Mn), or hepatic failure, and that the serum or whole blood Mn concentration is often increased.[1–3] T1 weighted MRI in these patients has shown hyperintensity, always in the bilateral globus pallidus and sometimes in part of the brainstem, although no abnormalities have been found on T2 weighted MRI. The Mn concentrations of CSF in these patients, however, have not been previously measured, because values in control subjects were previously undetermined. The present study was designed to investigate the CSF Mn concentrations in control subjects, and to evaluate the concentrations in patients with symmetric pallidal hyperintensities on T1 weighted MRI.

We examined five patients with the appropriate hyperintensity on T1 weighted MRI, aged from 31 to 72 years (mean 55.8 (SD 16.9) years); two with parenteral nutrition containing Mn (patients 1 and 2), two with Child's grade B cirrhosis (patients 3 and 5), and one without any specific factors relating to Mn or hepatic failure (patient 4, who had parkinsonism). In addition, we investigated 10 age matched control subjects without hyperintensity, aged from 28 to 78 years (mean 54.2 (SD 15.9) years) (table). The MRI was performed on a 1.5 Tesla magnet. In all five patients, T1 weighted MRI in the patients showed hyperintensity in the bilateral globus pallidus and in the region of the substantia nigra or the quadrigeminal plate, although T2 weighted MRI and brain CT showed no abnormalities. Ten control subjects from the neurology and psychiatry service with no history of parenteral nutrition containing Mn, or hepatic failure, showed no abnormal findings on T1 weighted MRI. We obtained blood and CSF samples from the five patients and 10 control subjects with informed consent. The serum, whole blood, and CSF Mn concentrations were measured by a standard method using graphite furnace atomic absorption spectrometry (Model VARIAN SPECTRA A-40) within 1 month after recognition of the symmetric pallidal hyperintensities. The CSF Mn concentrations were measured by diluting the sample with 0.5% (v/v) nitric acid to yield absorbance values within the linear range and injecting 200 µl into the furnace. The mean serum, whole blood and CSF Mn concentrations were calculated for the patients and control subjects. The non-parametric Mann-Whitney *U* test was used to assess the significance of differences between the two groups.

The serum, whole blood and CSF Mn concentrations of the patients and control subjects are listed in the table. All the serum and whole blood concentrations of the control group were within the normal range, and their CSF concentrations were mean 0.47 (SD 0.25)µg/l, a relatively narrow range. The CSF Mn concentration (2.1 µg/l) of patient 4, which was the lowest in the patient group, was much higher than 2 SD above the mean of the control group, but the serum Mn concentration of patient 4 and the whole blood Mn concentrations of patients 1, 3, and 4 were all within the normal range. The serum and CSF Mn concentrations of the patient group were significantly higher (p=0.023 and p=0.002 respectively) than

Serum, whole blood, and CSF Mn concentrations in five patients with hyperintensity on T1 weighted MRI and 10 control subjects without hyperintensity

	Age (y)	*Sex*	*Primary disease (parenteral Mn dose (mg/day)/duration (days))*	*Serum Mn (µg/l)*	*Whole blood Mn (µg/dl)*	*CSF Mn (µg/l)*
Patients:						
1	31	F	Pylonephritis (1.1/20)	1.7	1.6	6.7
2	46	F	Wernicke's encephalopathy (1.1/51)	2.1	4.4	3.8
2	64	M	Child's grade B cirrhosis	2.2	2.4	3.0
4	66	M	Parkinsonian syndrome	1.2	1.6	2.1
5	72	F	Child's grade B cirrhosis	2.3	4.2	3.1
Mean (SD)	55.8 (16.9)			1.90 (0.45)	2.84 (1.37)	3.74 (1.76)
Control subjects:						
1	28	F	Acute disseminated encephalomyelitis	1.5	1.7	0.7
2	40	M	Chorea-acanthocytosis	1.5	2.0	0.9
3	43	M	Multiple sclerosis	1.3	1.7	0.2
4	45	F	Neurosis	0.9	1.0	0.6
5	49	M	Guillain-Barré syndrome	1.9	2.0	0.4
6	57	F	Parkinsonian syndrome	1.0	1.3	0.6
7	61	F	Malignant syndrome	0.8	1.4	0.2
8	70	M	Progressive supranuclear palsy	0.9	1.1	0.3
9	71	M	Progressive supranuclear palsy	1.2	1.5	0.6
10	78	M	Parkinson's disease	1.3	2.8	0.2
Mean (SD)	54.2 (15.9)			1.23 (0.34)	1.64 (0.53)	0.47 (0.25)

Normal ranges: serum Mn 0.2-1.6µg/l; whole blood Mn 1.3-3.1µg/dl; CSF Mn concentrations have not been determined.

those of the control group, whereas the whole blood Mn concentrations were not significantly different (p=0.086) between the two groups.

This is the first study to evaluate the CSF Mn concentrations in patients with symmetric pallidal hyperintensities on T1 weighted MRI. Hyperintensity on T1 weighted MRI is associated with many factors, including calcification, lipid, haemorrhage, and Mn, but the pattern of MRI abnormalities in all the five patients was identical with that seen because of Mn deposition and the serum or whole blood Mn concentrations were often increased.[1–3] In the blood, Mn can bind to transferrin in the trivalent state and to albumin or α2-macroglobulin or low weight solutes in the divalent state. The blood Mn is transferred to the brain through the blood-brain barrier by several transport systems.[4] Recently, increased Mn concentrations were recognised in postmortem tissue samples from the brains of patients with long term parenteral nutrition containing Mn, or severe cirrhosis.[2 5] From our study, the CSF Mn concentrations were increased more than those in serum and whole blood in all patients and, in particular, patient 4, who had no parenteral nutrition or hepatic failure, showed an increase only in CSF Mn concentration. The CSF Mn concentrations are considered to reflect the accumulation of Mn in the brain tissue most directly of the three Mn concentrations. The reason why patient 4 is connected with Mn may be individual susceptibility.[6] Moreover, Mn neurotoxicity caused neuropsychiatric symptoms including pyramidal and extrapyramidal signs.[1–3] The findings suggest that a high degree of correlation exists between hyperintensity and the CSF Mn concentration, and that the increase may be a most useful marker and predictor of Mn neurotoxicity in patients with symmetric pallidal hyperintensities on T1 weighted MRI. Further studies with more patients are necessary to elucidate a precise correlation between Mn neurotoxicity and the CSF Mn concentration.

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CORRESPONDENCE

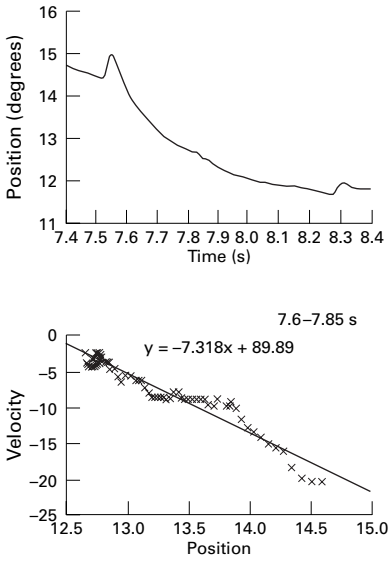
The role of the nucleus intercalatus in vertical gaze holding

I was interested to read the report of Janssen *et al*[1] of a patient with upbeat nystagmus who had had a medial medullary infarct. By contrast with our patient,[2] their patient had slow phases with a constant velocity, a "vestibular" type of nystagmus of central origin. As noted by Janssen *et al*, Hirose *et al*[3] have reported on a patient with a medial medullary infarct and upbeat nystagmus; some slow phases were exponential, some of constant velocity.

In the analysis of slow phases it is useful to plot eye velocity against position rather than plot eye position against time. In this representation, the plot of a vestibular type of slow phase with constant velocity is a horizontal straight line. However, when position varies exponentially with time, velocity is a linear function of position:

$$dx/dt = -kx,\ x = x_0\exp(-kt)$$

The gradient k is the decay constant. A regression line may be fitted and confidence limits for k established. A more detailed analysis[4] of the upbeat nystagmus in our patient with a medial medullary infarct confirmed that decay constants were significantly different from zero and therefore not "vestibular". However, the decay constants for the different slow phases varied and the plot of eye velocity against position seemed to be non-linear (figure). It is not surprising slow phases attributable to "integrator failure" might not be strictly exponential. The model of the perihypoglossal nuclei as a pure integrator rests on the assumption that the statics of the eye (the oculomotor plant) can be modelled by a pure "spring and dashpot",



Position-time and velocity-position plots of the slow phase of a vertical nystagmoid jerk.

second order linear differential equation.[5] This is an approximation for horizontal movements and a greater approximation for vertical eye movements. It also rests on the assumption that the anatomical connections are more simple than in reality. The variability of decay constants is consistent with the findings of Hirose *et al*.[3] This may reflect the varying activity of other afferents to the perihypoglossal nuclei. Nevertheless, the approximate linearity of the plots suggest that part of the function of the nucleus intercalatus, the most caudal of the perihypoglossal nuclei, is integration. Perhaps the reason that such a caudal structure may be involved in vertical integration is the need to coordinate vertical head position signals from cervical afferents with integrated head velocity signals from vestibular nuclei.

It would be of interest to know whether velocity–position plots of any of the slow phases of the patient of Janssen *et al*[1] show a non-zero gradient.

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Bronstein et al reply:

We thank Munro for his interest in the patient we reported in this *Journal* with a low medullary lesion and upbeat nystagmus.[1] The lesion probably involved the nucleus intercalatus, the lowermost part of the perihypoglossal nucleus, a nucleus thought to perform integration of ocular-motor signals. For the benefit of the general readership of this *Journal* we should like to clarify that the integration alluded to is mathematical integration. For instance, eye or head velocity signals arriving at such an integrator emerge as approximations of eye or head position signals. Currently accepted theories of ocular-motor function establish that a lesion to a gaze holding integrator produces nystagmus with slow phase velocity showing exponential decay. By contrast, peripheral vestibular lesions cause nystagmus with linear (constant) slow phase velocity.

The current discussion is centred on the findings in three recently reported patients with lesions probably involving the nucleus intercalatus.[1–3] The patients reported by Munro *et al*[2] and Hirose *et al*,[3] with large medullary lesions, had predominantly exponentially decaying slow phase velocity. Our patient, with a small paramedian lesion, had nystagmus with linearly decaying slow phase velocity.[1] Following Munro's suggestion we obtained velocity-position plots of single nystagmic beats and found most of them to be linear (horizontal line on velocity-position